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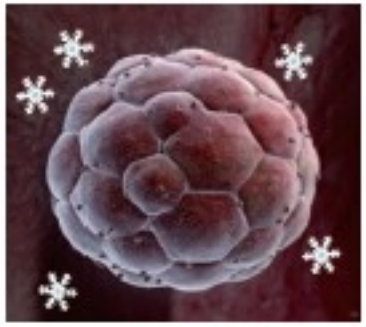

Optimizing Human Gamete and Embryo Freezing

GENOVA 13 GIUGNO 2014

PREPARAZIONE ENDOMETRIALE IN CICLO DI SCONGELAMENTO: SPONTANEO O INDOTTO?

Silvia Colamaria

g.en.e.r.a. ROMA
Clinica Valle Giulia

Oocyte and embryo cryopreservation

Cryopreservation of oocytes, embryos and blastocysts is an essential component of modern ART

Successful cryopreservation program:

1. allows to reduce the number of embryos transferred, thereby reducing multiple pregnancies and maximizing cumulative pregnancy rates per oocyte retrieval
2. allows delayed embryo transfer during a natural menstrual cycle reducing OHSS risks (cycle segmentation)
3. allows to preserve female fertility for medical or social reason

Human Reproduction, Vol.28, No.9 pp. 2425–2431, 2013
Advanced Access publication on June 11, 2013 doi:10.1093/humrep/det251

human reproduction ORIGINAL ARTICLE *Infertility*

Factors affecting the outcome of frozen–thawed embryo transfer

Zdravka Veleva[1,*], Mauri Orava[1], Sinikka Nuojua-Huttunen[2], Juha S. Tapanainen[1,3], and Hannu Martikainen[1]

Table IV Multivariate logistic regression analysis for live birth using the final adjusted model.

	P-value	OR (95.0% CI)
Embryo quality		
No top quality embryos frozen		Reference group
Top quality embryo(s)		
Frozen	0.02	1.85 (1.10–3.14)
Thawed	0.007	1.93 (1.20–3.11)
Transferred	<0.0001	3.41 (2.12–5.49)
Type of FET cycle		
Spontaneous, luteal support		Reference group
Spontaneous	0.003	0.58 (0.40–0.83)
Hormonal substitution	<0.0001	0.46 (0.31–0.69)
BMI	0.02	0.96 (0.92–0.99)
Two embryos versus one transferred	0.01	1.45 (1.08–1.94)
Overnight culture	0.07	1.37 (0.98–1.93)

LBRs after the transfer of a top quality embryo were similar in the FET (24.9%) and fresh cycles of the same period (21.9%). The chance of live birth increased significantly if ≥ 1 top quality embryo was present at freezing (odds ratio (OR) 1.85, 95% confidence interval (CI) 1.10–3.14), at thawing (OR 1.93, CI 1.20–3.11) or at transfer (OR 3.41, CI 2.12–5.48). Compared with spontaneous cycles with luteal support, purely spontaneous cycles (OR 0.58, CI 0.40–0.84) and hormonally substituted FET (OR 0.47, CI 0.32–0.69) diminished the odds of pregnancy. BMI (OR 0.96, CI 0.92–0.99) and transfer of two embryos versus one (OR 1.45, CI 1.08–1.94) were other factors that improved LBR after FET.

The development of embryo and endometrium should be synchronized

Natural cycle

spontaneous LH surge (NC FET)

HCG administration (modified-NC FET)

Artificial cycle

exogenous estradiol and progesterone (AC FET)
with or without GnRH-agonist co-treatment

Time synchronization of embryo transfer

NC-FET

Pregnancy rates are closely dependent on timely identification of ovulation and calculation of endometrial receptivity

(Harper, 1992; Tabibzadeh 1998)

LH monitoring in either blood or urine

Blood: rise in serum LH ➡ ovulation will occur 36-40 later

(Andersen, 1995)

Urine: LH surge lag up to 20-21 h behind the surge in blood

(Hoff, 1983; Frydman, 1984; Miller and Soules, 1996)

Time synchronization of embryo transfer

NC-FET

Problems associated with detection of spontaneous LH surge:

a. variation in time of its occurence between cycles and between patients *(Park, 2007)*

b. at least daily determination, better twice a day

(Miller and Soules 1996)

c. Large variation in thresholds of LH in urine kits and risk of up to 30% of false negative testing

(Guermandi, 2001; O'Connor, 2006)

Time synchronization of embryo transfer

Modified NC-FET

HCG triggering of ovulation to overcome LH monitoring:

a. no LH monitoring
b. 2-3 ultrasound evaluations of the dominant follicle
c. HCG administered when follicle is 17-18 mm
d. final oocyte maturation and ovulation will take place 36-38 h later *(Andersen, 1995)*

Time synchronization of embryo transfer

NC-FET vs modified NC-FET

There are no published studies comparing patient preference or cost-efficiency with regard to the different methods of monitoring in NC-FET. A properly conducted cost-efficiency calculation, also including patient preference, should be performed as part of a future RCT.

(Groenewoud et al, 2013)

Time synchronization of embryo transfer

NC-FET and modified NC-FET

Thawing and transfer of the embryo should be performed 3-5 days after ovulation depending on the stage of the embryo when it was frozen

(Nawroth and Ludwig, 2005; Paulson, 2011)

NC-FET: risk of unexpected ovulation and difficulty in planning thawing and transfer of the embryo

➡ cycle cancellation

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Time synchronization of embryo transfer

NC-FET

LH monitoring

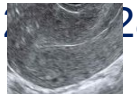
Blood pick

Urine pick

Progesterone supplementation (?)

1 2 3 4 5 6 7 8 9 10 12 13 14 15 16 17 18 19 20 21 22

23 28



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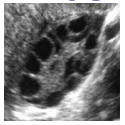

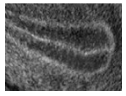

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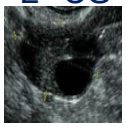

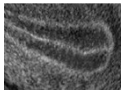

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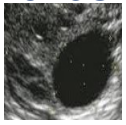

(OPU)

Day3 ET

Day5 ET

Modified NC-FET

HCG

Progesterone supplementation (?)

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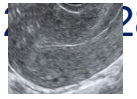
23 28



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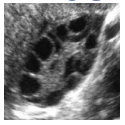

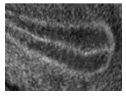

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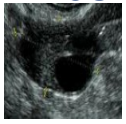

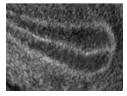

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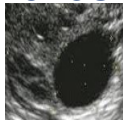

(OPU)

Day3 ET

Day5 ET

Modified NC and NC-FET: luteal phase supplementation?

No luteal support

Cryopreserved-thawed human embryo transfer: spontaneous natural cycle is superior to human chorionic gonadotropin–induced natural cycle

Human Mousavi Fatemi, M.D., Ph.D.,[a] Dimitra Kyrou, M.D.,[a] Claire Bourgain, M.D., Ph.D.,[b] Etienne Van den Abbeel, Ph.D.,[c] Georg Griesinger, M.D., Ph.D.,[d] and Paul Devroey, M.D., Ph.D.[a]

TABLE 3

Treatment outcomes in spontaneous LH and hCG group.

	Spontaneous LH (n = 61)	hCG group (n = 63)	Difference, % (95% CI)	*P* value
Ongoing pregnancy rate–ET (%)	31.1 (19)	14.3 (9)	16.9 (2.1–30.9)	.025
Miscarriage rate–ET (%)	0 (0)	3.2 (2)	−3.2 (−10.9 to 3.2)	NS
Biochemical rate–ET (%)	3.3 (2)	3.2 (2)	0.1 (−7.9 to 8.3)	NS
Positive hCG–ET(%)	34.4 (21)	20.6 (13)	13.8 (−1.9 to 28.7)	NS

Note: CI = confidence interval; NS = not significant.

Fatemi. Natural cycle vs. hCG induced for frozen ET. Fertil Steril 2010.

Conclusion(s): The results suggest the superiority of the natural cycle as compared with the natural cycle controlled by hCG administration in cryothawed ET cycles. (Fertil Steril® 2010;94:2054–8. ©2010 by American Society for Reproductive Medicine.)

Modified NC and NC-FET: luteal phase supplementation?

Luteal support

Reproductive BioMedicine Online (2011) 23, 484–489

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ARTICLE

Spontaneous ovulation versus HCG triggering for timing natural-cycle frozen–thawed embryo transfer: a randomized study

Ariel Weissman *, Eran Horowitz, Amir Ravhon, Zohar Steinfeld, Ravit Mutzafi, Avraham Golan, David Levran

Clinical and laboratory characteristics of fresh and frozen cycles and pregnancy and delivery rates were comparable for both groups. The number of monitoring visits in group A (3.2 ± 1.4) was significantly lower than in group B (4.7 ± 1.6) ($P = 0.002$). In patients undergoing NC-FET, triggering ovulation by HCG can significantly reduce the number of visits necessary for cycle monitoring without an adverse effect on cycle outcome. Ovulation triggering can increase both patient convenience and cycle cost effectiveness.

Modified NC and NC-FET: luteal phase supplementation?

Luteal phase progesterone increases live birth rate after frozen embryo transfer

Luteal support

Kerstin Bjuresten, B.S.,[a] *Britt-Marie Landgren, M.D., Ph.D.,*[a] *Outi Hovatta, M.D., Ph.D.,*[a] *and Anneli Stavreus-Evers, Ph.D.*[b]

	Progesterone	No progesterone	*P* value
No. of transfers	n = 219	n = 216	.8921
No. of embryos transferred	n = 290	n = 293	.9067
No. of embryos transferred (mean)	n = 1.32	n = 1.36	—
No. of single embryo transfers	n = 148	n = 139	.5423
No. of transfers with good-quality embryos	n = 164	n = 178	.3706
No. of transfers with lower-quality embryos	n = 126	n = 116	.3706
No. of blastocyst transfers	n = 3	n = 9	.1497
No. of IVF transfers	n = 110	n = 105	.7728
No. of ICSI embryos	n = 109	n = 112	.7728
Positive hCG rate	0.35 (76 of 219)	0.28 (60 of 216)	.1458
Miscarriage rate	0.03 (7 of 219)	0.03 (6 of 216)	.7977
Clinical pregnancy rate	0.32 (69 of 219)	0.25 (54 of 216)	.1614
Clinical abortion rate	0.02 (4 of 219)	0.05 (10 of 216)	.1105
Live birth rate (at least one live infant)	0.30 (65 of 219)	0.20 (44 of 216)	.0272*

Result(s): Live birth rate were significantly greater in women receiving vaginal progesterone as luteal phase support after frozen–thawed embryo transfer in natural cycles compared with those who did not take progesterone. There were no differences in biochemical pregnancy rate, pregnancy rate, or spontaneous abortion rate.

Conclusion(s): Progesterone supplementation improves live birth rate after embryo transfer in natural cycles.

(Fertil Steril® 2011;95:534–7. ©2011 by American Society for Reproductive Medicine.)

Modified NC and NC-FET: luteal phase supplementation

Luteal support
(retrospective study)

Human Reproduction, Vol.28, No.9 pp. 2425–2431, 2013
Advanced Access publication on June 11, 2013 doi:10.1093/humrep/det251

human reproduction ORIGINAL ARTICLE *Infertility*

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Compared with spontaneous cycles with luteal support, purely spontaneous cycles (OR 0.58, CI 0.40–0.84) and hormonally substituted FET (OR 0.47, CI 0.32–0.69) diminished the odds of pregnancy.

Modified NC and NC-FET: luteal phase supplementation?

Pregnancy loss after frozen-embryo transfer—a comparison of three protocols

Luteal support
(retrospective study)

Candido Tomás, M.D., Ph.D.,[a] Birgit Alsbjerg, M.D.,[b] Hannu Martikainen, M.D., Ph.D.,[c] and Peter Humaidan, M.D., D.M.Sc.[d]

NC-FET + luteal support vs modified NC no luteal support vs Artificial Cycle

Conclusion(s): A higher positive pregnancy test rate was obtained in E + P frozen ET cycles in comparison with other protocols; however, due to an increased preclinical and clinical pregnancy loss, comparable clinical pregnancy, and delivery rates are reported for the three protocols. (Fertil Steril® 2012;98:1165–9. ©2012 by American Society for Reproductive Medicine.)
Key Words: FET, frozen embryo transfer, substituted cycles, pregnancy loss, luteal support

Modified NC and NC-FET: luteal phase supplementation?

Human Reproduction Update, Vol.19, No.5 pp. 458–470, 2013
Advanced Access publication on July 2, 2013 doi:10.1093/humupd/dmt030

human reproduction update

What is the optimal means of preparing the endometrium in frozen–thawed embryo transfer cycles? A systematic review and meta-analysis

Eva R. Groenewoud[1,*], Astrid E.P. Cantineau[1], Boudewijn J. Kollen[2], Nick S. Macklon[3], and Ben J. Cohlen[4]

"Based on the conflicting results of the previously mentioned studies we

conclude that currently there is too little evidence supporting a positive

Time synchronization of embryo transfer

Artificial cycle (AC-FET)

Estrogen (E_2) and progesterone (P) in sequential regimen:

a. E_2 causes endometrial proliferation and suppression of the development of the dominant follicle

b. when endometrial thickness is 7-9 mm on US, P is added to initiate secretory changes *(Dor, 1991; El-Toukhy, 2008)*

c. embryo thawing and transfer is planned according to the moment of P supplementation *(Dor, 1991; Jaroudi 1991)*

Time synchronization of embryo transfer

AC-FET with GnRH-FET

E_2 and P in sequential regimen after GnRH-a desensitization

a. E_2 administration does not guaratee complete pituitary suppression and dominant follicle may occur

b. should spontaneous ovulation occur, the endometrium is maybe exposed to P earlier ➡ incorrect timing of thawing and transferring

GnRH-agonist co-treatment

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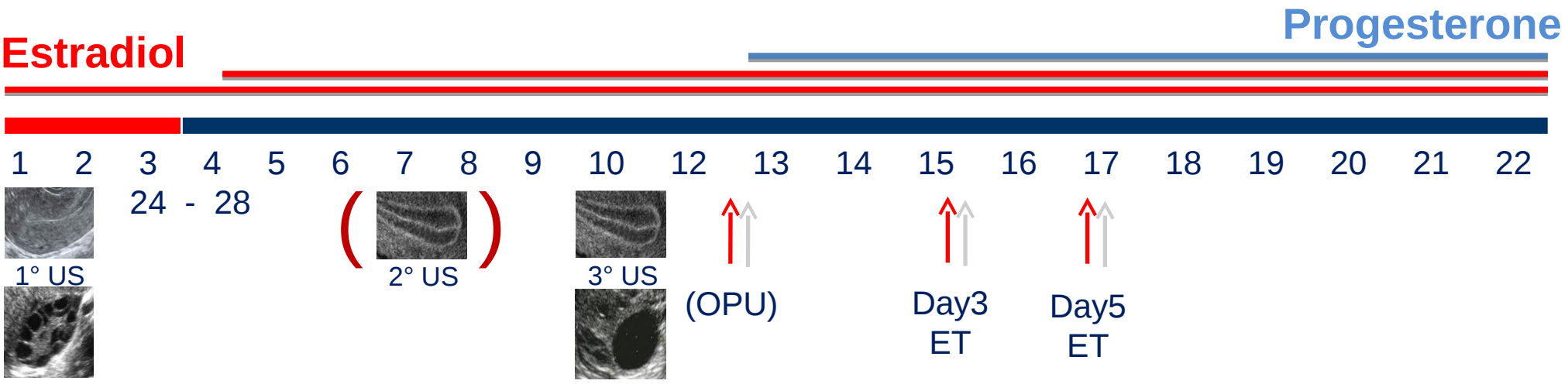
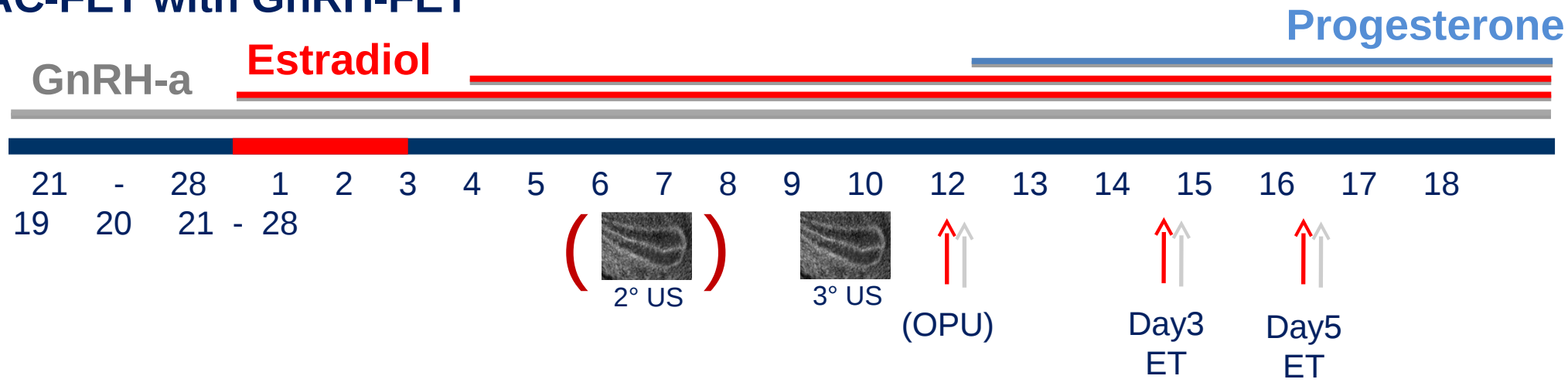
Time synchronization of embryo transfer

AC-FET



AC-FET with GnRH-FET



Time synchronization of embryo transfer

AC-FET with or without GnRH-FET **vs NC-FET**

Pros

- cycles easier to plan making it popular among many doctors
- patients with anovulatory cycles

Cons

- medication needed → less “physiological”

Is any one of these approaches superior to another

?

Cycle regimens for frozen-thawed embryo transfer (Review)

Ghobara T, Vanderkerchove P

Ghobara T, Vanderkerchove P. Cycle regimens for frozen-thawed embryo transfer. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD003414. DOI: 10.1002/14651858.CD003414.pub2.

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Main results

Seven randomised controlled studies assessing six comparisons and including 1120 women in total were included in this review.

1) O + P FET versus natural cycle FET: this comparison demonstrated no significant differences in outcomes but confidence intervals remain wide, and therefore moderate differences in either direction remain possible (OR 1.06, 95% CI 0.40 to 2.80, P 0.91).

2) GnRHa plus day O plus day P FET versus O plus day P FET: this comparison showed that the live birth rate per woman was significantly higher in the former group (OR 0.38, 95% CI 0.17 to 0.84, P 0.02). The clinical pregnancy rate was also higher but not significantly so (OR 0.76, 95% CI 0.52 to 1.10, P 0.14).

3) O plus day P FET versus follicle stimulating hormone (FSH) FET, 4) O plus day P FET versus clomiphene FET and 5) GnRHa plus day O plus day P FET versus clomiphene FET: there were no differences in the outcomes in the comparison of these cycle regimens.

6) Clomiphene plus day human menopausal gonadotrophin (HMG) FET versus HMG FET: in a comparison of two ovulation induction regimes the pregnancy rate was found to be significantly higher in the HMG group (OR 0.46, 95% CI 0.23 to 0.92). There were also fewer cycle cancellations and a lower multiple pregnancy rate when HMG was used without clomiphene but these did not reach statistical significance.

Authors' conclusions

At the present time there is insufficient evidence to support the use of one intervention in preference to another.

Human Reproduction Update, Vol.19, No.5 pp. 458–470, 2013
Advanced Access publication on July 2, 2013 doi:10.1093/humupd/dmt030

human reproduction update

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Eva R. Groenewoud[1,*], Astrid E.P. Cantineau[1], Boudewijn J. Kollen[2], Nick S. Macklon[3], and Ben J. Cohlen[4]

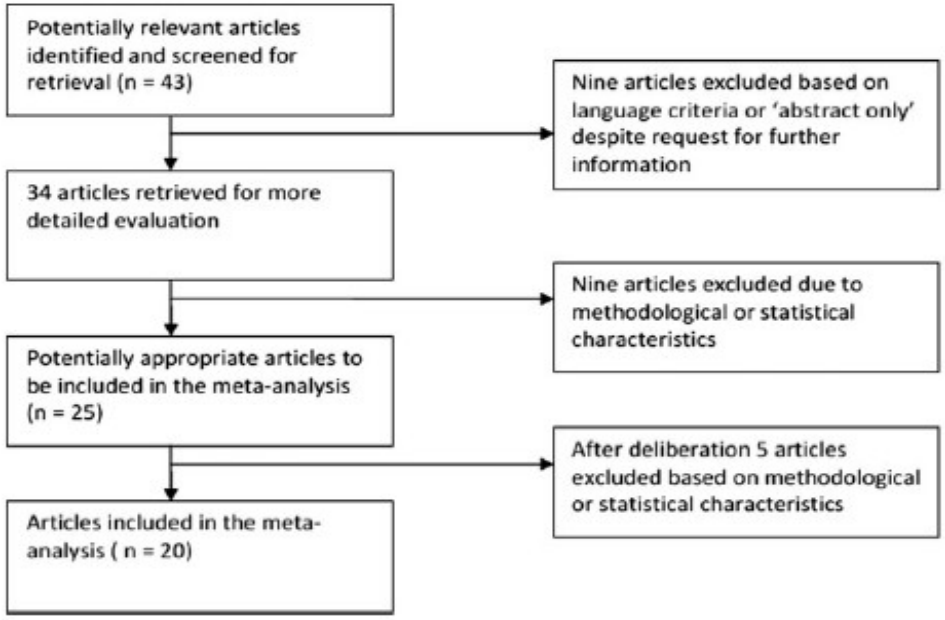

Figure 1 Flowchart for inclusion of studies on methods of preparing the endometrium in FET cycles for systematic review and meta-analysis.

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Table I Overview of studies included in a meta-analysis to determine the optimal means of preparing the endometrium in FET cycles in patients undergoing IVF.

Study and year	Design	Population	Allocation	Outcome
True NC versus modified NC				
Chang et al. (2011)	Retrospective cohort	644 cycles (tNC 310, mNC 130, AC 204), ovulatory patients	Preference, costs	CP/OP
Fatemi et al. (2010)	RCT	124 cycles (tNC 61, mNC 63), ovulatory patients	Concealed allocation, non-blinded	OP
Tomax et al. (2012)	Retrospective cohort	4470 cycles (tNC 1019, mNC 444, AC 2858), ovulatory and anovulatory patients	Preference, cycle characteristics	CP/LB
Weissman et al. (2009)	Retrospective cohort	132 cycles (tNC 71, mNC 61), ovulatory patients	Preference	CP/LB
Weissman et al. (2011)	RCT	55 cycles (tNC 30, mNC 25), ovulatory patients	Concealed allocation non-blinded	CP/OP/LB
NC versus AC				
Cattoli (1994)	RCT	100 cycles (AC 56, NC 44), ovulatory patients	Not stated	CP
Chang et al. (2011)	Retrospective cohort	644 cycles (tNC 310, mNC 130, AC 204), ovulatory patients	Preference, costs	CP/OP
Givens et al. (2009)	Retrospective cohort	807 cycles (NC 602, AC 205), ovulatory and anovulatory patients	Preference, cycle characteristics	CP/LB
Hancke et al. (2012)	Retrospective cohort	203 cycles (NC 148, AC 55), ovulatory and anovulatory patients	Not stated	CP
Kawamura (2007)	Retrospective cohort	856 cycles (NC 720, AC 136), ovulatory patients	Preference	ChP/CP/LB
Loh and Leong (1999)	Retrospective cohort	212 cycles (NC 51, AC 161), ovulatory patients	Preference	CP/LB
Morozov et al. (2007)	Retrospective cohort	242 cycles (AC 174, NC 68), ovulatory patients	Not stated	CP
Tomax et al. (2012)	Retrospective cohort	4470 cycles (tNC 1019, mNC 444, AC 2858), ovulatory and anovulatory patients	Preference, cycle characteristics	CP/LB
Xiao et al. (2011)	Retrospective cohort	1020 cycles (NC 380, AC 640), ovulatory and anovulatory patients	Preference, cycle characteristics	CP/OP
NC versus AC with GnRH				
al Shawaf et al. (1993)	Retrospective cohort	149 cycles (AC 72, NC 77), ovulatory and anovulatory patients	Age, cycle characteristics	CP
Gelbaya et al. (2006)	Retrospective cohort	417 cycles (NC 212, AC + GnRH 205), ovualtory patients	Changed protocol	CP/LB
Hill et al. (2010)	Retrospective cohort	1391 cycles (NC 240, AC + GnRH 1151), ovulatory and anovulatory patients	Preference, cycle characteristics	ChP/CP/LB
Queenan et al. (1994)	Retrospective cohort	528 cycles (NC 398, AC + GnRH 230), ovulatory and anovulatory patients	Cycle characteristics	CP/OP
Tanos et al. (1996)	Quasi-randomized	304 cycles (NC 219, AC + GnRH 85), ovulatory and anovulatory patients	Preference, cycle characteristics	CP
AC versus AC with GnRH				
Dal Prato et al. (2002)	RCT	296 cycles (AC 150, AC + GnRH 145), ovulatory patients	Concealed allocation, non-blinded	CP
El Toukhy et al. (2004)	RCT	234 cycles (AC 117, AC + GnRH 117), ovulatory patients	Concealed allocation, non-blinded	CP/LB
Simon et al. (1998)	RCT	106 cycles (AC 53, AC + GnRH 53), ovulatory and anovulatory patients	Not stated	CP/OP

NC-FET vs modified NC-FET

1965 cycles

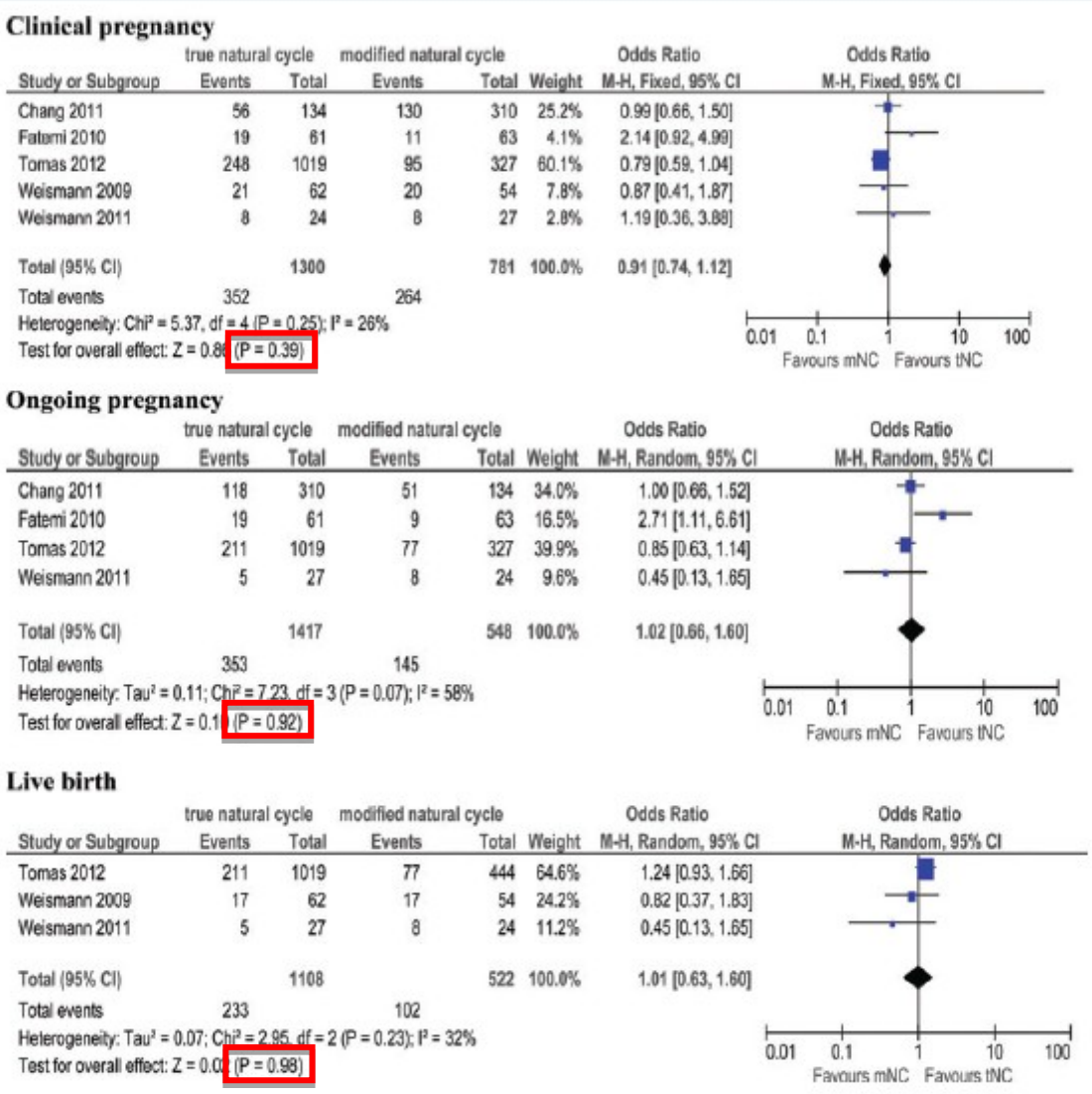


Figure 2 True NC versus modified NC: pooled result of all studies.

NC-FET vs modified NC-FET: luteal phase support

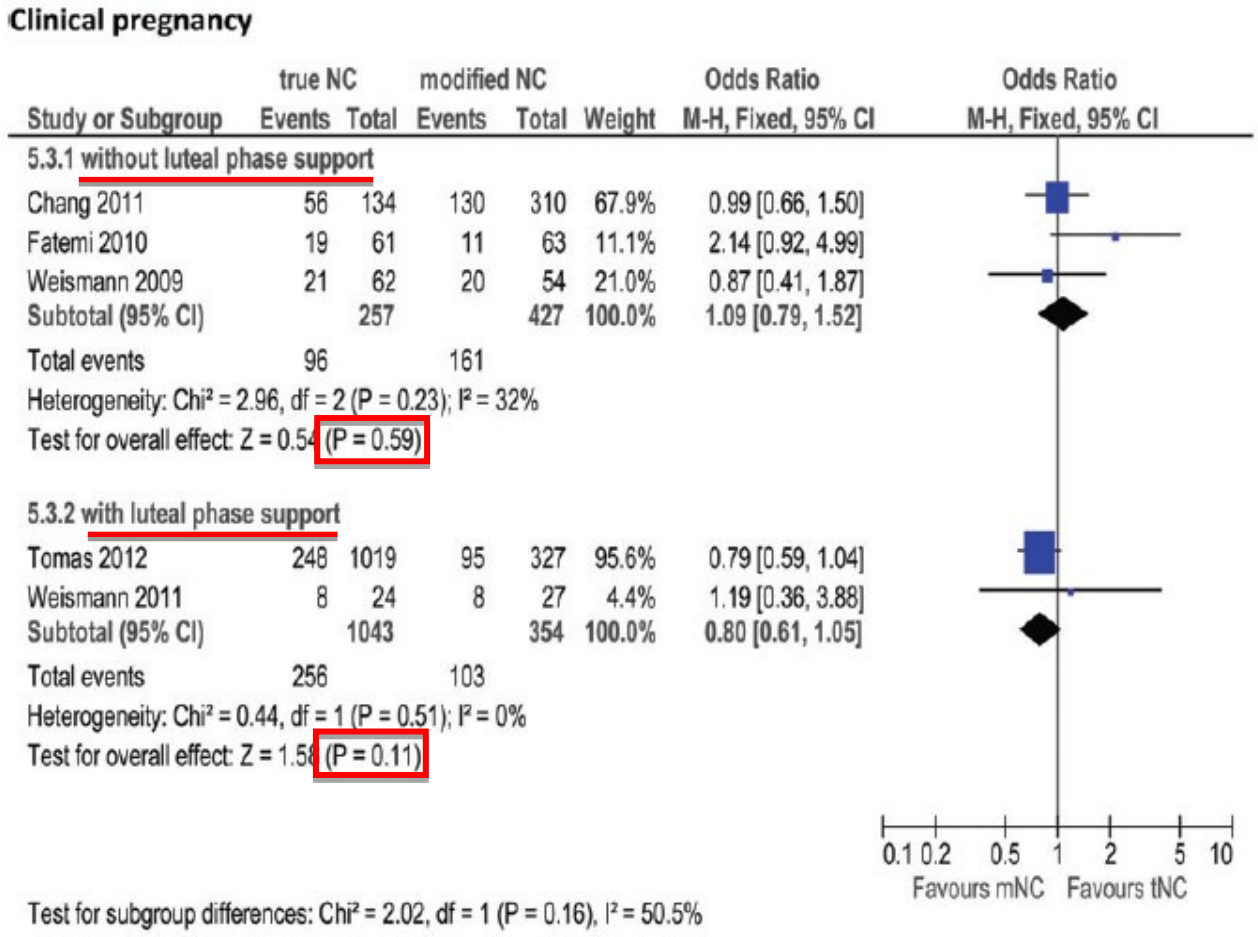


Figure 3 True versus modified NC: subgroup analysis based on luteal phase support.

NC-FET vs modified NC-FET: luteal phase support

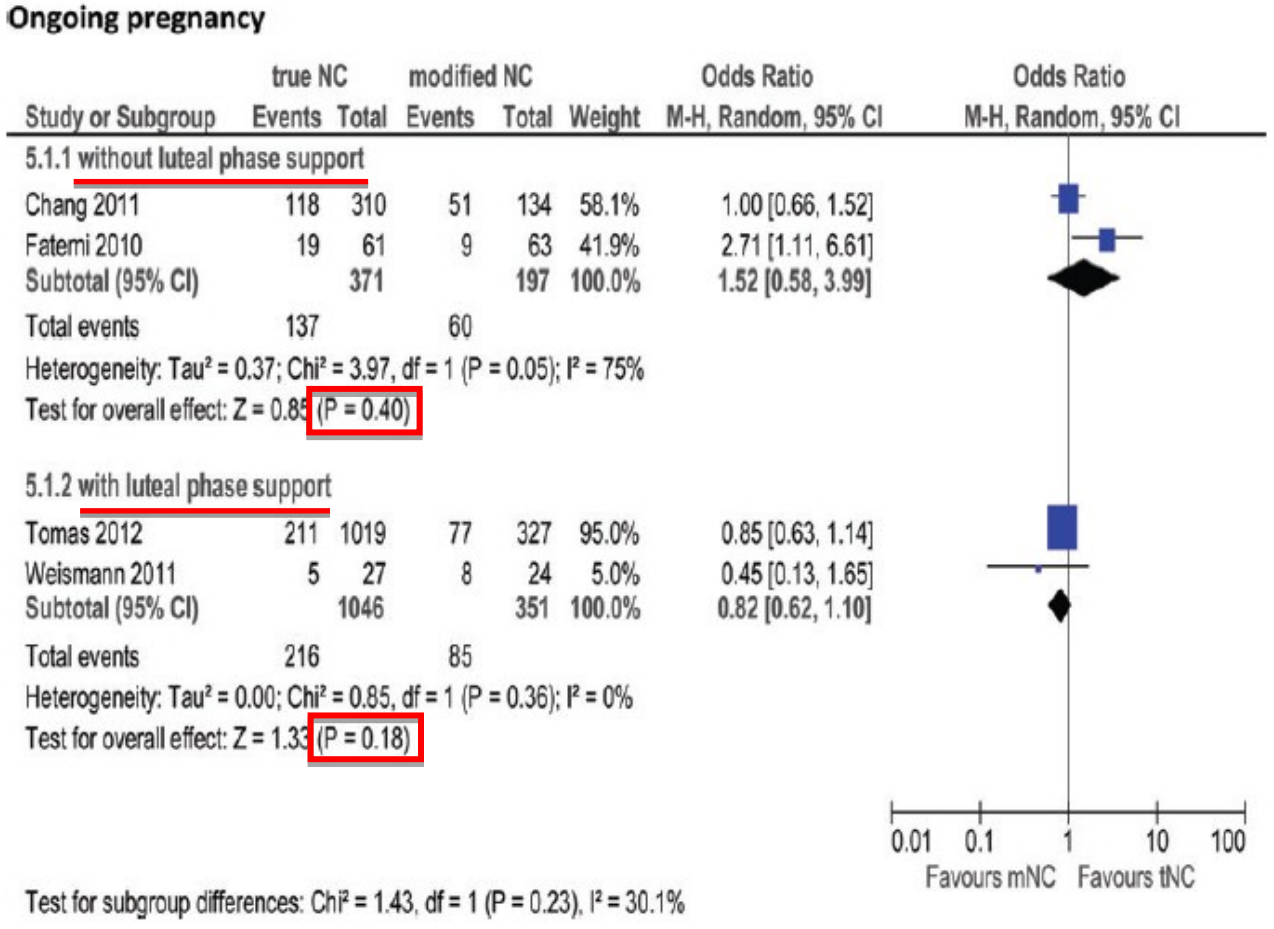


Figure 3 True versus modified NC: subgroup analysis based on luteal phase support.

NC-FET vs AC-FET

8152 cycles

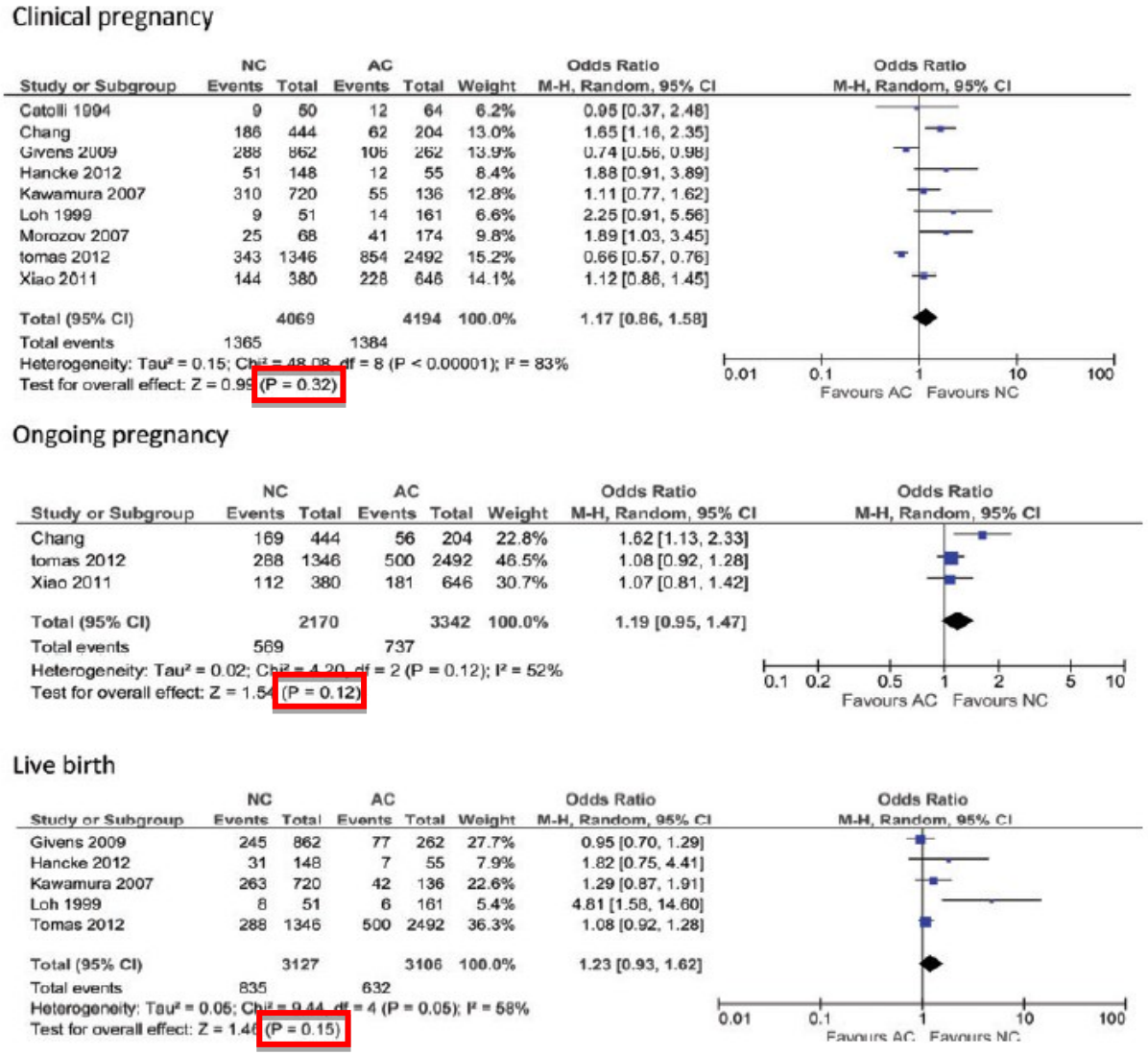


Figure 4 NC versus AC.

NC-FET vs AC-FET: true NC or modified NC

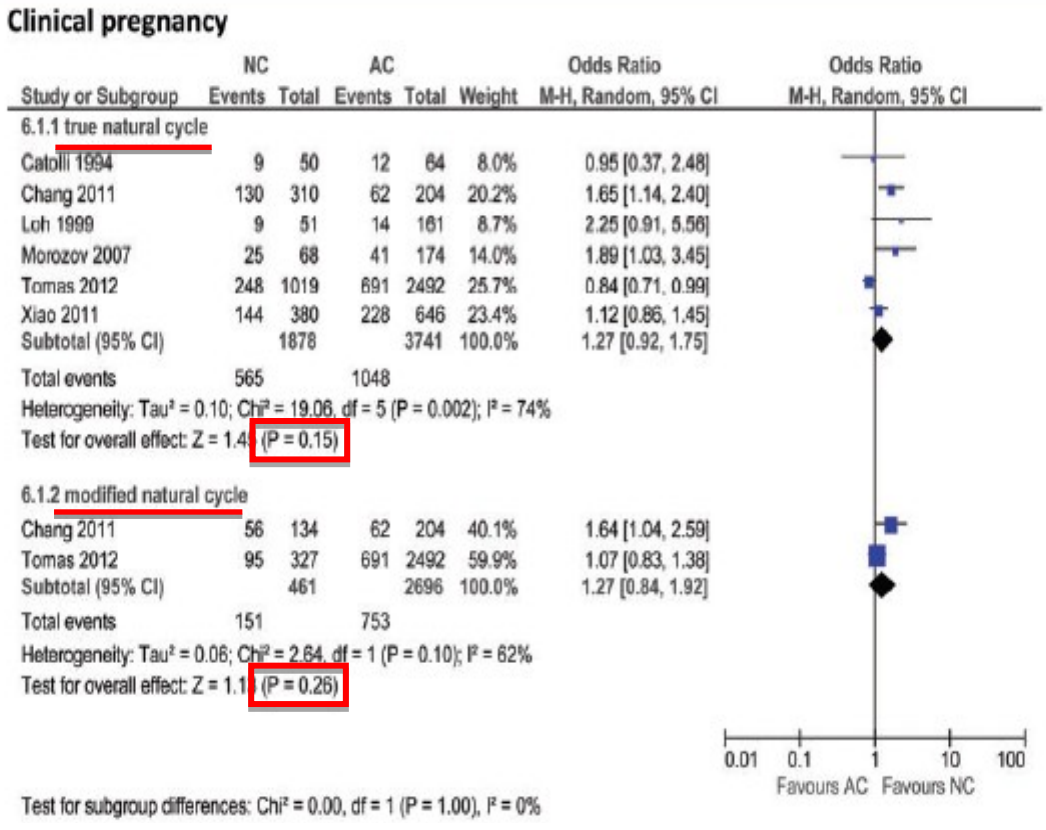


Figure 5 NC versus AC: subgroup analyses based on modified or NC.

NC-FET vs AC-FET: true NC or modified NC

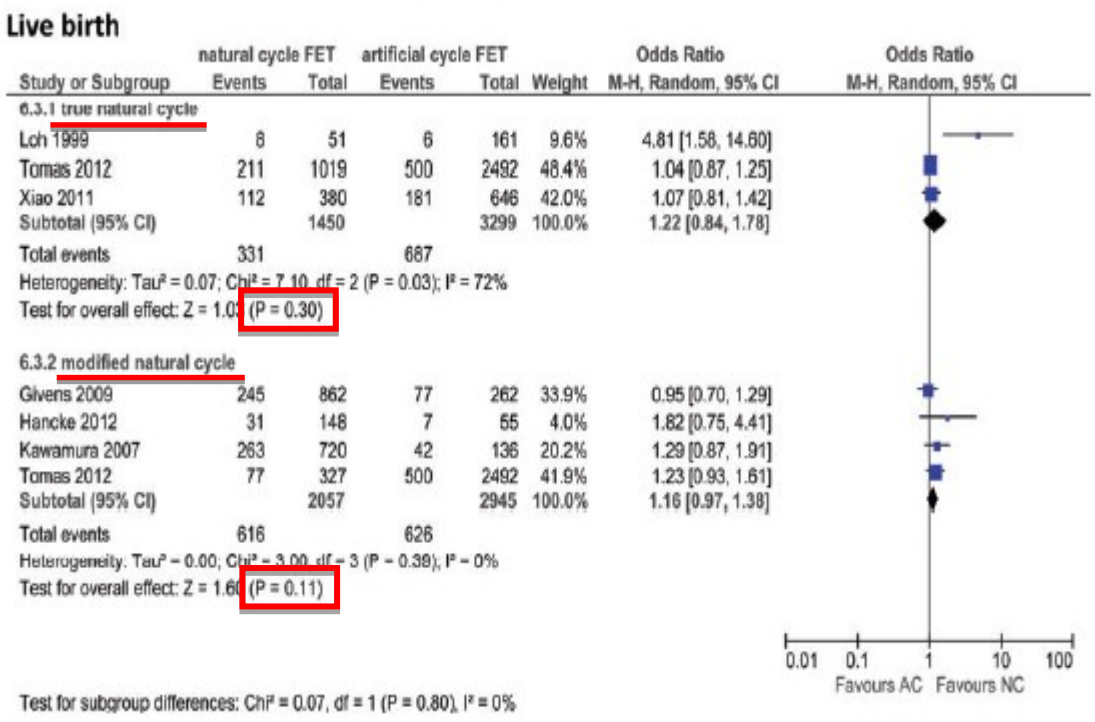


Figure 5 NC versus AC: subgroup analyses based on modified or NC.

NC-FET vs AC-FET: NC-luteal support or no support

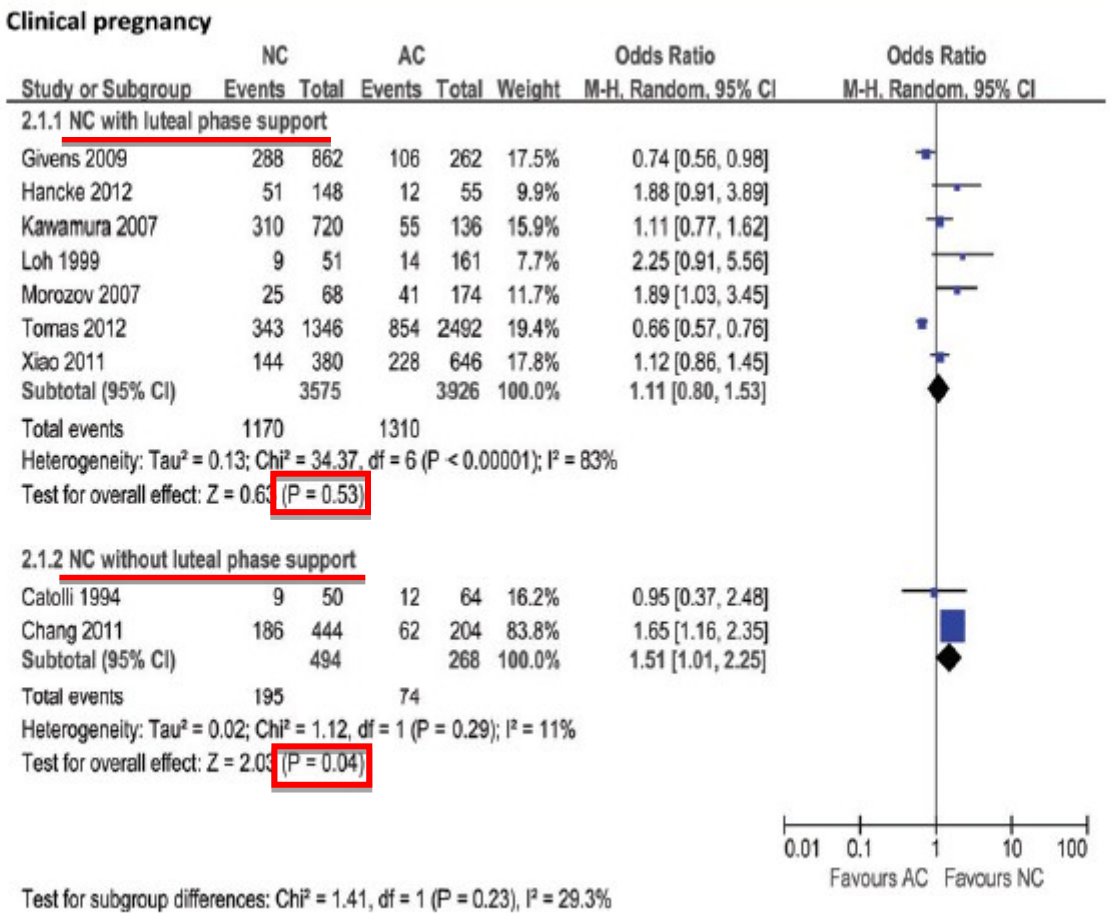


Figure 6 NC versus AC: subgroup analyses based on luteal phase support.

NC-FET vs AC-FET with GnRH agonist

2789 cycles

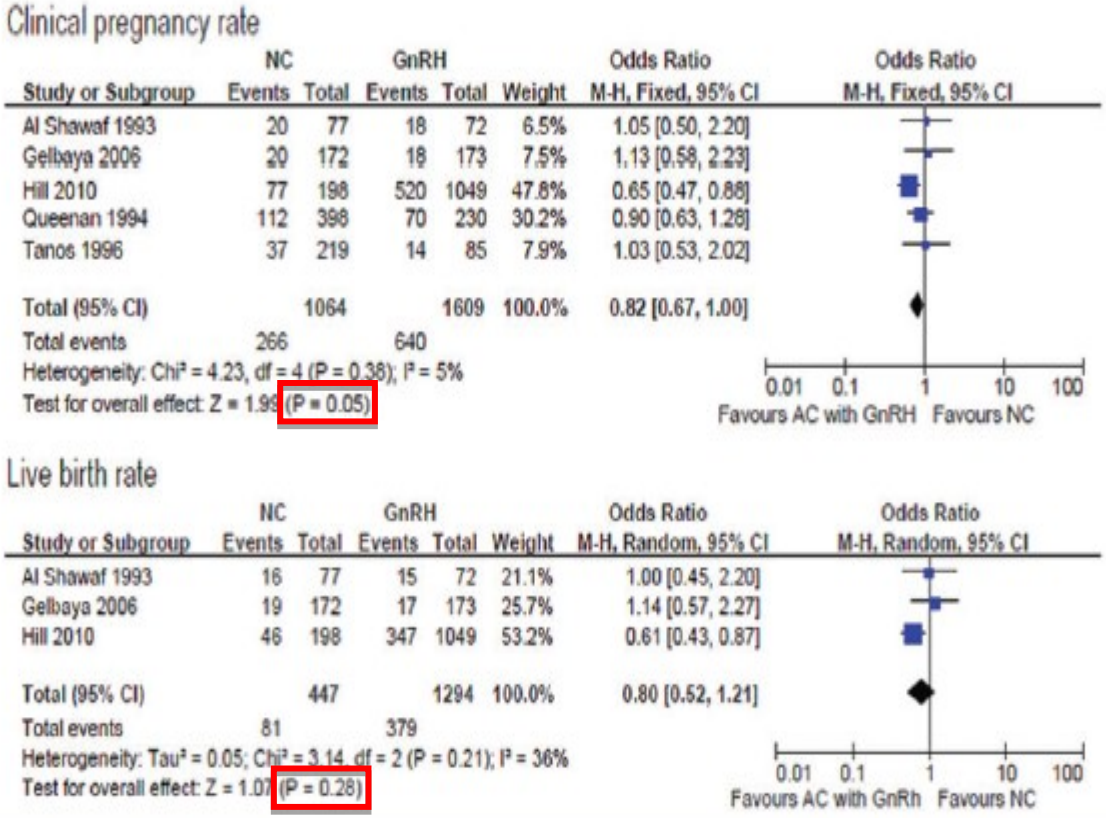
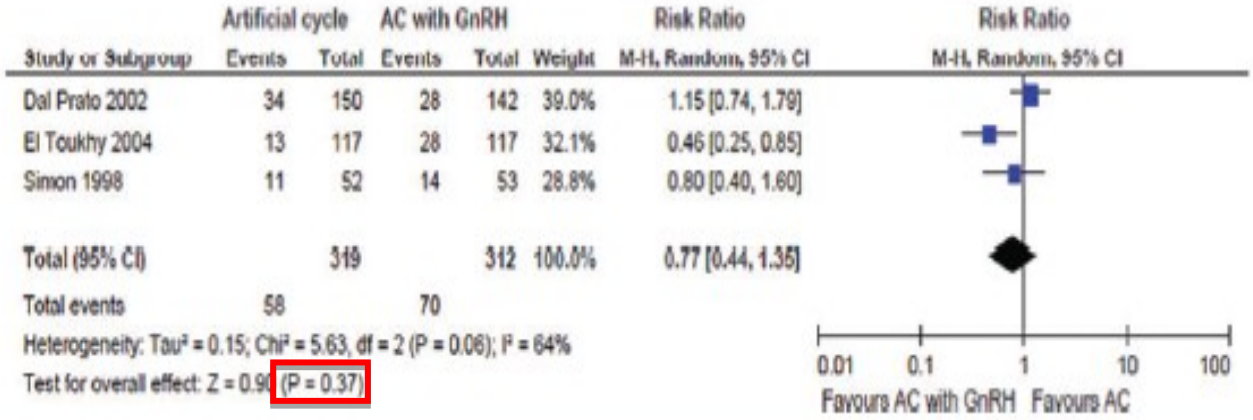


Figure 7 NC versus AC with GnRH agonist.

AC-FET vs AC-FET with GnRH agonist

631 cycles



Study or Subgroup	Artificial cycle Events	Total	AC with GnRH Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Dal Prato 2002	34	150	28	142	39.0%	1.15 [0.74, 1.79]
El Toukhy 2004	13	117	28	117	32.1%	0.46 [0.25, 0.85]
Simon 1998	11	52	14	53	28.8%	0.80 [0.40, 1.60]
Total (95% CI)		319		312	100.0%	0.77 [0.44, 1.35]
Total events	58		70			

Heterogeneity: Tau² = 0.15; Chi² = 5.63, df = 2 (P = 0.06); I² = 64%

Test for overall effect: Z = 0.90 (P = 0.37)

Figure 8 AC versus AC with GnRH agonist.

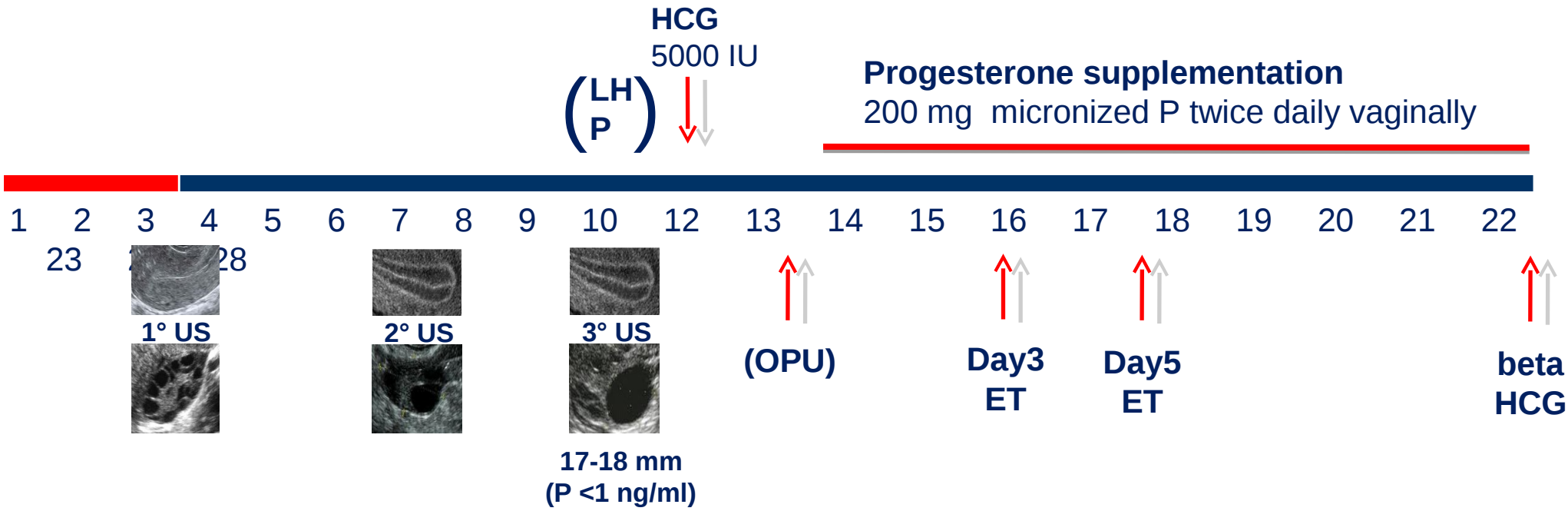
human reproduction update

What is the optimal means of preparing the endometrium in frozen–thawed embryo transfer cycles?

We conclude that it is not possible, based on the current published literature, to recommend one endometrial preparation method in FET over another. The number of RCTs is limited and small numbers of patients are included. Future prospective RCTs should not only address pregnancy rates but also consider convenience and cost efficiency.

Therefore, there remains a need for prospective randomized studies to clarify which approach, if any, may improve clinical pregnancy rate after FET, which is the most efficient and cost-effective, and which is associated with the lowest patient burden. Only then can the optimal approach be discerned.

FET cycles: endometrial preparation GENERA 2009-2012



N. of FET cycles (total)	1422
N. Oocyte warming cycles (%)	503 (35)
N. Embryo warming cycles (%)	919 (65)
N. Modified NC (%)	1381 (97)
N. Artificial Cycles (AC) (%)	41 (3)

Warmed cycles clinical outcomes: GENERA 2009-2012 (up to 42 y)

	Oocyte Warmed Cycle	Embryo Warmed Cycle
N of cycles	503	919
N of patients	373	715
Female Age (mean±SD)	36.4±4.1	36.9±3.8
Warmed Oocytes/Embryos	2064	1746
Survival rate (%)	1828/2064 (88.5)	1696/1746 (97.1)
N of ET (%)	437/503 (86.8)	900/919 (97.9)
Transferred embryo (mean±SD)	2,10±0,8	1.86±0.9
Clinical PR per Cycle (%)	131/503 (26.0)	267/919 (29.0)
Clinical PR per ET (%)	131/437 (29.9)	267/900 (29.7)
Implantation Rate	142/919 (15.4)	280/1680 (16.6)
Delivery Rate per warmed cycle (%)	106/503 (21.0)	231/919 (25.1)
Delivery Rate per Embryo transfer	106/437 (24.2)	231/900 (25.6)

Thank you for your attention

g.en.e.r.a.

CLINICA VALLE GIULIA, Roma

CLINICAL DIRECTOR: Filippo Maria Ubaldi

LABORATORY DIRECTOR: Laura Rienzi

Silvia Colamaria
Maddalena Giuliani
Enrica Gravotta
Fabio Sapienza

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Marta Stoppa

biroma

Annalise Giallonardo
Mauro Schimberni

cipa centro italiano procreazione assistita

Michele Ermini
Beatrice Ermini

www.generaroma.it
colamaria@generaroma.it